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REVIEW

The Biological Contributions to Gender Identity and Gender Diversity: Bringing Data to the Table

Tinca J. C. Polderman[1,2] · Baudewijntje P. C. Kreukels[3,4] · Michael S. Irwig[5] · Lauren Beach[6,7] · Yee-Ming Chan[8,9] · Eske M. Derks[10] · Isabel Esteva[11,12] · Jesse Ehrenfeld[6,13,14,15,16] · Martin Den Heijer[4,17] · Danielle Posthuma[1,2] · Lewis Raynor[18] · Amy Tishelman[8,19] · Lea K. Davis[6,20,21,22,23] · on behalf of the International Gender Diversity Genomics Consortium

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Abstract
The American Psychological Association defines gender identity as, "A person's deeply-felt, inherent sense of being a boy, a man, or a male; a girl, a woman, or a female; or an alternative gender (e.g., genderqueer, gender nonconforming, gender neutral) that may or may not correspond to a person's sex assigned at birth or to a person's primary or secondary sex characteristics" (American Psychological Association, Am Psychol 70(9):832–864, 2015). Here we review the evidence that gender identity and related socially defined gender constructs are influenced in part by innate factors including genes. Based on the data reviewed, we hypothesize that gender identity is a multifactorial complex trait with a heritable polygenic component. We argue that increasing the awareness of the biological diversity underlying gender identity development is relevant to all domains of social, medical, and neuroscience research and foundational for reducing health disparities and promoting human-rights protections for gender minorities.

Keywords Gender identity · Transgender · Gender dysphoria · Heritability · Genetics · Twin studies

Introduction

The concept of gender identity, the inner psychological experience of gender, was first formalized and published in 1968 by Dr. Robert Stoller, who hypothesized that "sex and gender are not inevitably bound… each may go in its quite independent way" (Stoller 1968). Though the experience of gender is as old as humanity itself, the modern conceptualization of gender identity is still developing. For the sake of clarity in this review, we will defer to the definition put forth by the American Psychological Association (2015), which states that gender identity is, "a person's deeply-felt, inherent sense of being a boy, a man, or a male; a girl, a woman, or a female; or an alternative gender (e.g., genderqueer, gender nonconforming, gender neutral) that may or may not correspond to a person's sex assigned at birth or to a person's primary or secondary sex characteristics" (American Psychological Association 2015). In 2016, the National Institutes of Health recognized the significant health disparities facing individuals whose gender identity does not match their sex assigned at birth and formally designated gender minorities as a health disparity population for research purposes.

The goal of this review is to provoke thoughtful consideration of the crucial role that human genetics can play in making society more open and equitable for gender minorities. We have performed a comprehensive, structured literature review on the heritability of gender identity, gender nonconformity, and related constructs to evaluate evidence that genetic influences are among the biological factors that influence variation in gender identity. We hypothesize that gender identity is a multifactorial complex trait with a heritable polygenic component. Recognizing the significant social impact of genomic science, we provide historical and social context for our structured review of the genetics of gender identity. Finally, we discuss a possible path forward for socially responsible genomic research that is inclusive

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✉ Lea K. Davis
lea.k.davis@vanderbilt.edu

Extended author information available on the last page of the article

of gender minorities, with the aim of reducing health and social disparities.

Gender identity

Every person has a gender identity. Children typically become aware of gender between the ages of three and five (Ruble et al. 2007). The terminology used to describe one's gender identity is rapidly evolving and includes man, woman, pangender, agender, bigender, genderqueer, and androgyne, among dozens of additional descriptors. Often gender identities are classified into "cisgender" and "transgender" umbrellas. Cisgender is used to refer to a gender identity that matches a person's sex assigned at birth (i.e., sex determined by examination of genitals at birth, or through genetic testing). Transgender refers to a gender identity that differs from the sex assigned at birth. The term "gender minority" is used by the NIH to refer to transgender populations as well as those who do not consider themselves transgender but whose gender identity and expression vary from traditional, societal, or cultural norms. It is important to note that gender *identity* is not the same as gender *role*, gender *expression*, or sexual orientation, though they may be correlated (Box 1). For example, an individual may identify as a cisgender male but reject a stereotypical male gender role. Transgender and cisgender people may identify as heterosexual, bisexual, homosexual, or other sexual orientations.

A recent national survey reported that approximately 0.6% of Americans (1.4 million individuals) identify as transgender, consistent with European estimates ranging from 0.8% for assigned males to 1.1% for assigned females (Bakker et al. 1993; Kuyper and Wijsen 2014; Reed et al. 2009). It has been suggested that such estimates are likely an underrepresentation of the true prevalence of transgender identity given the stigma gender minorities face. When an individual applies/is referred for transgender health care, (s) he may receive a diagnosis based on fulfillment of DSM-5 criteria for gender dysphoria. Prevalence studies are often based on the number of individuals that have a diagnosis or have received gender confirming treatment. However, many transgender individuals may not apply for medical treatment. Also, due to stigma, they may not reveal their feelings of gender incongruence in epidemiologic studies in the general

Box 1 Key terms and definitions of gender identity and related concepts. We note that many of these concepts are still evolving and attempts to define them precisely are problematic at best. Nevertheless, we offer these definitions for interpreting the results of studies reviewed in this paper

- *Sex assigned at birth*—For the majority of births, a relative, midwife, doula, nurse or physician inspects the genitalia of the infant upon delivery and assigns the female sex or male sex based on this observation. Typically, sex is treated as binary, but exceptions may occur in some medical and/or cultural contexts (e.g., an infant with ambiguous genitalia). Throughout the paper, sex assigned at birth is also referred to as "male-assigned sex", "assigned male", "female-assigned sex", or "assigned female"
- *Sexual orientation*—(American Psychological Association) An enduring pattern of emotional, romantic, and/or sexual attractions
- *Gender identity*—(American Psychological Association) A person's deeply-felt, inherent sense of being a boy, a man, or a male; a girl, a woman, or a female, or an alternative gender (e.g., genderqueer, gender nonconforming, gender neutral) that may or may not correspond to a person's sex assigned at birth or to a person's primary or secondary sex characteristics
- *Gender incongruence of adolescence or adulthood* (ICD-11 Beta Draft)—is characterized by a marked incongruence between an individual's experienced/expressed gender and the assigned sex in pre-pubertal children. It includes a strong desire to be a different gender than the assigned sex; a strong dislike on his or her sexual anatomy or secondary sex characteristics and/or a strong desire for the primary and/or secondary sex characteristics that match the experienced gender. The incongruence must have persisted for about 2 years, and can only be diagnosed in adolescents and adults
- *Gender dysphoria*—(World Professional Association for Transgender Health) Diagnosis given to indicate distress resulting from a difference between a person's gender identity and the person's sex assigned at birth and the associated gender role and/or primary and secondary sex characteristics. – see WPATH Standards of Care, 7th Version
- *Gender expression*—(Winter et al. 2016) The way in which a person expresses their gender identity, sometime through appearance, dress, or behavior
- *Gender role*—(World Health Organization) Culturally-specific set of behavioral expectations often (but not always) defined by male and female designations
- *Gender stereotype*—(United Nations Human Rights Office) A general preconception about characteristics, features, and/or roles that are or should be possessed by women and men
- *Gender minority*—(National Institutes of Health) includes individuals whose gender identity differs from the sex originally assigned to them at birth; whose gender expression varies significantly from what is traditionally associated with or typical for that group; and/or who vary from or reject traditional cultural conceptualizations of gender in terms of male–female dichotomy. This group includes people who label themselves (or are labeled) as transgender, transsexual, cross-dressers, and/or Two-Spirit
- *Cisgender*—(Merriam-Webster Dictionary) of, relating to, or being a person whose gender identity corresponds with the sex the person was assigned at birth
- *Transgender*—(World Professional Association for Transgender Health) An adjective to describe a diverse group of individuals who self-identify as a gender minority or whose gender identity is different (in varying degrees) from the sex assigned to them at birth

population. Nevertheless, an increasing number of individuals are engaging the health care system for gender-affirming care (Aitken et al. 2015; Beek et al. 2016; de Vries et al. 2015; Editorial 2011; Institute of Medicine 2011; Kuehn 2011; Reed et al. 2009; Zucker 2017; Zucker et al. 2008).

Historical and current social context

To understand the current social environment in which studies of biological and psychosocial contributions to gender identity are conducted, it is important to be aware of the history of such research. The scientific research community has historically played a significant role in pathologizing gender non-conformity and rationalizing interventions now widely rejected as harmful on the basis of current consensus regarding gender diversity. There exists a body of literature from the 1960s through the 1980s which propagated an erroneous nosology of gender nonconformity, gender dysphoria, and varied gender expression as mental illnesses caused by absent fathers and overbearing mothers (Marantz and Coates 1991; Rekers et al. 1983; Stevenson and Black 1988). Researchers and clinicians developed conversion and aversion behavior-modification methods aimed primarily at extinguishing feminine mannerisms and characteristics in young boys (see Box 2). Importantly, research into the biological contributions to gender identity also has the potential to pathologize gender nonconformity as a mental illness or "disease". Acknowledging the history of research into gender diversity is an important first step towards ensuring that the same mistakes, for example conducting research without the input of the community being studied, are not repeated.

Box 2 Historical Vignette

Historical Vignette
An active area of research in the late 1970s was the development of behavior-modification methods that included training parents to punish or withhold attention and affection when their young sons displayed what researchers described as "effeminate behaviors". In one such study (1974), the mother of four year old Kraig was trained to "extinguish feminine behavior (verbal and play)" by following instructions given to her by experimenters over earphones such as, "stop talking to him now," "ignore him now," and "look away from him."
"When Kraig began to tantrum or engage in other uncooperative behaviors (he typically did when his mother ignored him), the experimenter was particularly supportive of the mother. In fact, when the mother first withdrew her attention for Kraig's feminine play, he put so much "pressure" on her (by alternating between crying and aggressing at her) to reinstate the attention, that we had to terminate the session and ask Kraig to leave for a minute. Before sending Kraig back to the playroom, we reassured the mother empathetically that she was doing the right thing and was doing it well, and that we would continue to be available in the observation room to assist her." (Rekers and Lovaas 1974)

While attitudes about gender variance has changed tremendously in the past decade, we must be mindful of the tensions that continue to exist. For example, while professional healthcare organizations recognize the need for many transgender people to change their bodies to match their identity, most medical systems require a diagnosis before physicians can bill insurance companies to cover these services. During a healthcare encounter in the United States, individuals with gender minority status may receive a diagnosis of gender dysphoria (ICD9 302.85, ICD10 F64.*) which then has implications for clinical care and insurance coverage. The gender dysphoria diagnosis includes DSM-5 criteria used to indicate the presence of distress associated with incongruence between gender identity and sex assigned at birth. While useful for clinical and billing purposes, this diagnosis can be highly stigmatizing. Therefore, tensions continue to exist over how to classify gender incongruence to both depathologize gender non-conforming expressions and identities and to guarantee access to transgender health care in complex medical systems across the world (Beek et al. 2016; Drescher et al. 2016a, b; Winter et al. 2016). We believe that research on the genetics of gender identity has the potential to reduce stigma of transgender and gender-variant individuals by highlighting the continuous, not dichotomous, nature of gender identity.

The polygenic threshold model

We will briefly introduce the polygenic threshold model as it relates to complex traits and enthusiastically direct any reader wishing a more comprehensive discussion of the topic to an excellent review (Visscher and Wray 2015). In brief, the model asserts that many genes contribute to—but do not determine—complex traits. Studies have shown that most complex traits are multifactorial and polygenic, meaning that hundreds or thousands of genetic variants, each with individually small effects, contribute additively to trait variance along with other non-genetic factors (Cortes-Cortes et al. 2017; Fernandez et al. 2015, 2014a, b; Gratten et al. 2014; Gusev et al. 2013, 2014; Shi et al. 2016). This stands in contrast to monogenic or oligogenic traits in which fewer than a dozen genes account for the majority of the genetic contribution to the trait. Under the polygenic threshold model, contributing factors assume a continuous normal distribution in the population. In other words, while any two people may have very different phenotypes (e.g., gender identities), the entire population exists along a single spectrum with no clear divisions (e.g., no line between "cis" and "trans" identities). We hypothesize that gender identity is complex, multifactorial, and polygenic meaning that many genetic factors likely contribute to the development of gender identity through complex interactions with

many environmental factors. In recent years this model profoundly changed our conceptualization of neuro-diverse traits such as autism spectrum disorders (ASDs), which were once considered rare and dichotomous (i.e., affected or not-affected). ASDs are now recognized as a true spectrum with some people displaying many autistic traits (and carrying many associated genetic variants), some people displaying few autistic traits (and carrying few associated genetic variants), and most people falling somewhere in between (and carrying some associated genetic variants). This model has been inherently destigmatizing because it demonstrates that, in terms of genetics, there is no "us" and "them" (Kendler 2015). Another important corollary of this model is that no single genetic variant (or set of genetic variants) could reliably distinguish between people of varying gender identities.

Heritability studies

As in most complex traits, family and twin-based heritability studies provide the first evidence that genetic factors contribute to the development of gender identity and gender-related constructs. Heritability (h^2) is defined as the proportion of the phenotypic variation that arises from genetic influences. Environmental influences explain the other part of this variation, and are divided into shared (i.e., environmental influences shared by individuals in a sampled population), and non-shared environmental influences (i.e., environmental influences experienced uniquely by each individual and measurement error). To disentangle the genetic and environmental effects on trait variation, data derived from twin and adoption designs provide useful information. Most heritability studies have been twin studies, as the twin design is one of the most powerful designs to estimate genetic and environmental effects (Polderman et al. 2015; van Dongen et al. 2012). The rationale of the twin design is that monozygotic (MZ) twins, being genetically identical, share all genetic effects, both additive and non-additive (i.e., interaction between alleles within and across genes). In contrast, dizygotic (DZ) twins share on average 50% of their additive and 25% of their non-additive genetic effects. In the classical twin design, heritability estimates are based on the phenotype comparison within MZ and DZ twins. Genetic influences are indicated when the average within MZ pair similarity is larger than the average within DZ pair similarity (usually quantified as 'twin correlations'; rMZ and rDZ) and a simple calculation can be used to estimate the heritability: 2*(rMZ-rDZ) (Falconer 1965). More refined estimates of trait-heritability incorporate pathway analysis, structural equation modeling, and variance components (Knopik et al. 2016). Based on the twin correlations, a variance components model is applied to the data to decompose the total variance into additive genetic (A), non-additive genetic (D), and common environmental (C) effects. Non-shared environmental (E) effects contain measurement error and are therefore always included in the models. Heritability estimates of complex traits can vary widely from approximately 20% for self-reported loneliness (Gao et al. 2017) to approximately 80% for height (Ge et al. 2017). Most complex behavioral traits demonstrate heritability in the range of 30−60% (Polderman et al. 2015).

Literature review methodology

Here, we review available twin studies that report heritability estimates on gender dysphoria and related phenotypes across different ages divided in three sections, covering studies in children, adolescents, and adults (age groupings used by the studies). We conducted a literature review in PubMed using the following search terms*, ("English"[Language] AND ("1900/01/01"[Date—Publication]: "2017/04/25"[Date—Publication]) AND twin AND "humans"[Filter] AND 'gender'[Title/Abstract] AND (heritability[Title/Abstract] OR "genetic influence"[Title/Abstract] OR "environmental influence"[Title/Abstract] OR "genetic factors"[Title/Abstract] OR "environmental factors"[Title/Abstract]) AND "journal article"[Publication Type] (NOT review[Title] NOT review[Publication Type]).

This search produced 302 publications, the abstracts of which were then manually reviewed for relevant content, resulting in the identification of 11 heritability studies (Table 1). The criteria for inclusion were (a) Gender identity and/or gender nonconformity was measured with instruments validated for gender identity or related constructs, (b) MZ and DZ twin pairs were included, and (c) twin correlations and/or a heritability estimate was reported; one additional study reported on the increased prevalence of gender dysphoria among siblings in families with a proband (~4 times the population rate) but did not report a heritability estimate (Gomez-Gil et al. 2010) and thus was not included in the systematic review. Of the 11 that met criteria for our systematic review, four exclusively studied adults, one included adults and adolescents, three included children and adolescents, and three focused on children. All reports but one included both individuals assigned male and individuals assigned female sex at birth. Two studies examined gender dysphoria explicitly while the others focused on related, but not identical, phenotypes. It is important to note the limitations of the instruments used to measure gender identity. We must recognize the possibility that they may conflate true gender identity with gender expression. To clarify the different measures, we made a distinction between those attempting to measure (1) gender role/expression/behavior (GR) versus (2) transgender identity or gender dysphoria. As described in Box 1, gender role, expression, and behavior

Table 1 Heritability estimates from published studies of gender identity and related constructs

Study	Phenotype and GR or GI	Instrument	Child or adult	Sample sex assigned at birth	Country	Heritability
1. Bailey et al. (2000)	Childhood gender nonconformity (GR) Continuous gender identity (GI)	Retrospectively, 24 items from *For males* Gender identity scale for males, the childhood play activities checklist, the recalled childhood gender behaviors questionnaire and the physical aggressiveness scale *For females* Childhood play activities checklist, the recalled childhood gender behaviors questionnaire, and the masculine gender identity scale	Adults Males N = 1341 pairs Females N = 2441 pairs	Males and Females	Australia	Childhood gender nonconformity Males 50% Females 37% Continuous gender identity Males 31% Females 24%
2. Burri et al. (2011)	Childhood gender typicality (GR) Adult gender identity (GI)	Four items retrospectively assessing childhood sex-typed behavior and gender identity	Adults Females N = 4426 individuals	Females	United Kingdom	Childhood gender typicality: 32% Adult gender identity: 11%
3. Beijsterveldt et al. (2006)	Cross gender behavior (GR) and cross gender identity (GI)	Two items from child behavior checklist: 'behaves like opposite sex'; 'wishes to be of opposite sex'	Children Age 7 Males N = 7202 individuals Females N = 7395 individuals Age 10 Males N = 4266 individuals Females N = 4530 individuals	Males and Females	The Netherlands	Age 7: 77% Age 10: 71%
4. Coolidge et al., 2002	Gender identity disorder (GI)	Six GID items based on criteria DSM	Children and adolescents N = 157 pairs	Males & Females	United States	62%
5. Iervolino et al. (2005)	Sex typed behavior (GR)	24 items of Pre-school activities inventory (PSAI; Golombok and Rust 1993a, b)	Children Males N = 1854 pairs Females N = 1913 pairs	Males Females	United Kingdom	Males 34% Females 57%

Table 1 (continued)

Study	Phenotype and GR or GI	Instrument	Child or adult	Sample sex assigned at birth	Country	Heritability
6. Knafo et al., 2005	Masculinity/ femininity (GR)	24 items of pre-school activities inventory (PSAI; Golombok and Rust 1993a, b)	Children Males N = 2789 pairs Females N = 3010 pairs	Males Females	United Kingdom	Males Femininity 17% Females Masculinity 40%
7. Lippa and Hershberger (1999)	Masculine instrumentality Feminine expressiveness Gender diagnosticity (GR)	Personality questionnaire, and items on daily interests, activities, and occupation	Adults Males N = 320 pairs Females N = 480 pairs	Males and Females	United States	Masculine instrumentality: 36% Feminine Expressiveness: 38% Gender Diagnosticity: 53%
8. Loehlin and Martin (2000)	Masculinity/ femininity (GR)	Items of personality questionnaires for which males differed from females (i.e., 'Worried', 'Reserved', and 'Breaks rules')	Adults Older cohort Males N = 1807 individuals Females N = 3487 individuals Younger cohort Males N = 1148 individuals Females N = 1858 individuals	Males Females	Australia	Older cohort Males Worried: 41% Reserved: 38% Breaks rules: 27% Older cohort Females Worried: 46% Reserved: 43% Breaks rules: 36% Younger cohort Males Worried: 34% Reserved: 28% Breaks rules: 28% Younger cohort Females Worried: 36% Reserved: 37% Breaks rules: 34%

Table 1 (continued)

Study	Phenotype and GR or GI	Instrument	Child or adult	Sample sex assigned at birth	Country	Heritability
9. Loehlin et al. (2005)	Gender diagnosticity (GR)	Items of personality questionnaires for which males differed from females	Adolescents Males N = 1048 individuals Females N = 1040 individuals Adults Males N = 3254 individuals Females N = 6958 individuals	Males and Females	Australia, United States (US)	Adult Australians Males 47% Females 44% Adolescent Australians Age 12 Boys 43% Girls 42% Age 14 38% Age 16 30% US Elderly 36% Adults 28% Adolescents Boys 25% Girls 38%
10. Mitchell et al. (1989)	Masculinity/ femininity (GR)	1. Adolescent Self-Perception Inventory (ASPI) 2. Children's Personality Attributes Questionnaire (CPAQ)	Children Adolescents N = 70 pairs	Males & Females	United States	ASPI Masculinity 46% ASPI Femininity 30% CPAQ Masculinity 48% CPAQ Femininity 20%
11. Sasaki et al. (2016)	Gender Identity Disorder, assessed with questionnaire items, based on DSM-IV (GI)	Gender identification 1. 'I wish to be the opposite gender' 2. 'I wish to be treated as the opposite gender' Gender dysphoria 1. 'I feel discomfort with my own gender' 2. 'I feel discomfort with my body's gender characteristics'	Children and Adolescents and Adults Males N = 1961 pairs Females N = 2333 pairs	Males and Females	Japan	Males Children 15% Adolescents 0% Adults 0% Females Children 84% Adolescents 41% Adults 11%

Heritability estimates are reported based on sex assigned at birth if provided in the original study. Heritability estimates are reported based on sex assigned at birth if provided in the original study

GR gender role/expression/behavior, *GI* gender identity or related construct (i.e., gender dysphoria)

are distinct from gender identity, and societal influences are evident across these constructs.

About half of the studies investigated "masculinity" and "femininity." In brief, these constructs imply that masculinity and femininity are exclusive endpoints of one dimension. Masculinity is defined in terms of being 'aggressive, dominant, and independent' and femininity in terms of being 'warm, sensitive, and nurturant'. Masculinity and femininity are usually measured with items reflecting sex-specific behaviors, feelings, or even cultural stereotypes as part of personality questionnaires (e.g., "I am often the leader among my friends", or "I am a kind and gentle person"). The one-dimensional approach has been criticized as many other less stereotypic characteristics that might also be highly relevant to conceptions of masculinity or femininity are missing in the standard measures. To address this issue, and acknowledge population and time specific indicators of masculinity or femininity, the concept of 'gender diagnosticity' was introduced by Lippa in various studies (e.g., (Lippa 1991, 1995). A gender diagnosticity score is computed using discriminant analysis of a much broader set of predictive indicators that optimally discriminates membership of two groups. Instead of a categorical male/female assignment, gender diagnosticity is a Bayesian probability that an individual is male or female on the basis of gender-related indicators. This method is described in more depth in Lippa and Hershberger (1999).

Findings of heritability studies

Findings in adults

Lippa and Hershberger (1999) studied a relatively large sample of 839 MZ and DZ same-sex twin pairs on measures of masculinity, femininity and gender diagnosticity as defined by Lippa and Hershberger (1999). For masculinity as well as femininity, the MZ twin correlations were around 0.35 while DZ twin correlations were about half of the MZ correlation. Subsequent analyses showed heritability estimates of 36% for masculinity and 38% for femininity, meaning that about one-third of the variation in masculinity and femininity among male assigned and female assigned twins respectively was explained by genetic factors, and two-thirds by environmental factors or measurement error. No effects of shared environmental influences were observed; thus all environmental effects were unique influences, which includes factors such as measurement error. For gender diagnosticity, a heritability of 53% was reported. Similar findings were observed for masculinity as well as femininity in a study by (Loehlin and Martin 2000), when they investigated a sample of older (N = 2647 pairs, mean age 41.2) and a sample of young (N = 1503 pairs, mean age 23.2) Australian twins with heritability estimates of around 40% in the older cohort, and around 35% in the younger cohort. In a large study by (Loehlin et al. 2005), samples of different ages (adolescents and adults) and nationalities (i.e., Australia and the United States) were assessed on gender diagnosticity. Results were quite similar across samples, and confirmed previous studies. Again, DZ correlations were about half the MZ correlations, suggesting no shared environmental influences, and substantial genetic influences ranging from 23 to 47% were observed.

Childhood and current (adult) gender identity and non-conformity were investigated by (Bailey et al. 2000) in a large sample of Australian twins, and by (Burri et al. 2011) in a more recent British study, in assigned females only. To compare the findings of both studies, we first focus on assigned female results. Within this group, childhood gender identity was heritable ($h^2 = 24$ and 32%) as was adult gender identity ($h^2 = 31$ and 11%) in Bailey et al. (2000) and in Burri et al. (2011), respectively. This suggests that genetic factors contribute to the variation in gender identities among both adults and children. The findings in assigned males as reported by Bailey were somewhat higher ($h^2 = 50\%$) than in assigned females ($h^2 = 37\%$) in the same study for childhood gender identity while the heritability estimate for adult gender identity among assigned males in Bailey ($h^2 = 31\%$) was closer to their assigned female estimate ($h^2 = 24\%$), suggesting that adult gender identity is similarly heritable regardless of sex assigned at birth. In conclusion, these studies suggest that variation in gender-related measures in adults are mostly explained by genetic and unique environmental effects, while the shared environmental effects (i.e., cultural factors) are negligible.

Findings in adolescents

Masculinity and femininity were also investigated in a study in American children and adolescents by (Mitchell et al. 1989). Their study comprised a small sample of 38 MZ and 32 DZ twin pairs with an age range of 8–15 years old. Masculinity and femininity in this study were assessed with two self-reports: the Adolescent Self-Perception Inventory (ASPI) and Children's Personality Attributes Questionnaire (CPAQ) which are, as expected, correlated (r = 0.36). Masculinity and femininity appeared to be heritable at this age, with heritability estimates for masculinity being substantially higher (~47%) compared to femininity (~25%).

Environmental effects that were not shared explained the remaining part of the variance. Two studies in children and adolescents focused on gender identity and non-conformity measured by questionnaire. In both studies, the questions were drawn from the DSM-IV criteria for gender identity disorder (GID), which was substantially revised in the DSM-5 due in part to a problematic focus on gender roles, particularly among children. (Coolidge et al. 2002) asked

parents of 96 MZ pairs and 61 DZ pairs, with an age range of 4–17 years, to complete six questionnaire items drawn from the GID criteria and present on the Coolidge Personality and Neuropsychological Inventory; (Coolidge and Segal 1998) in order to assess 'GID symptomology'. To account for potential age differences, the sample was divided in a younger and older cohort, but genetic analyses showed that merging these data did not lead to increased heterogeneity. Variation in questionnaire scores could be explained by a model including genetic and unique environmental influences but also by a model including shared and unique environmental influences. In other words, this study lacked statistical power to distinguish between environmental and genetic effects. A recent study by (Sasaki et al. 2016) in Japanese twins also examined mean "GID trait scores" (not diagnoses) in a large sample (N = 4354 twin pairs), aged 3–27 years old. In this study, the trait scores were based on four questionnaire items drawn from the DSM-IV criteria for GID. The sample was divided into children, adolescents, and adults, and the analyses were specific to sex assigned at birth. Among those assigned male sex at birth, of all three age groups the majority of the variance was explained by environmental factors, although in children and adolescents all component estimates (genetic and environmental) had large confidence intervals that all encompassed zero, suggesting that there was not enough statistical power to demonstrate any factors as clear contributors. In contrast, the data of those assigned female sex at birth showed a large contribution of genetic variance, particularly in children ($h^2 = 0.84$) and adolescents ($h^2 = 0.41$). Of note, again most estimates had wide confidence intervals that also spanned zero. The authors explain the large amount of environmental variance and lack of statistical power in males, compared to females, by asserting that 'in Japan females can more easily express their gender dysphoria and cross-gender identification than males'. Overall, the studies in adolescents show both effects of genetic factors and effects of the shared environment. However, the statistical significance of the shared environmental effects is not robust and likely reflects some level of confounding of gender identity with gender non-conformity and gender roles. This is in contrast with the studies in adults which demonstrate negligible effects of shared environment.

Findings in children

Two studies in children used data from 3- and 4 year-old twins from the Twin Early Development study (TEDs, N > 3000 twin pairs) in the UK. One study examined 'sex-typed behavior' (Iervolino et al. 2005), and one study used data on 'atypical gender development' (Knafo et al. 2005). In addition, both studies used 24 items of the Pre-School Activities Inventory (PSAI), an instrument which measures masculinity and femininity, and samples were partly overlapping; thus the two studies are not completely independent. The study by Iervolino et al. also surveyed siblings of twins to disentangle twin-specific environmental effects from 'real' shared environmental effects. Their results showed that variation in PSAI scores for boys could be explained by variation in heritability (34%), shared environment (29%), twin-specific environment (22%), and unique environment (15%). For girls these estimates were, respectively, 57, 0, 22, and 21%. Knafo et al. separated the PSAI femininity score in boys versus masculinity score in girls. They observed in boys a heritability of 17%, while shared environmental variation explained 67%, and in girls a heritability of 40% with an estimate of 45% for the shared environmental variation. Thus, again the estimate for shared environmental variation is higher in boys versus girls, while the heritability shows the opposite pattern (higher in girls vs. boys). In a large longitudinal study in 7 and 10-year old Dutch twins, two items of the Child Behavior Checklist were summed (i.e., 'behaves like opposite sex' and 'wishes to be of opposite sex') to measure cross-gender behavior and cross-gender identity (van Beijsterveldt et al. 2006). No differences in heritability were observed between the sexes (male and female sex assigned at birth). At age 7 the estimates for genetic and unique environmental variance were 77 and 23%, respectively for male and female sex assigned at birth, and at age 10 these were 71 and 29% respectively. In large contrast to the other studies as described above, no significant effects of the shared environment were detected.

In summary, studies in children are scarce and the findings thus far are conflicting, with two large but dependent studies showing substantial effects of the shared environment, and one large independent study showing no such effects. This may be due in part to developmental timing of gender identity, the diversity of instruments used to measure gender self-concepts, differences in the underlying constructs being measured by each instrument, and weaker influence of genetic effects influencing gender identity in childhood.

Molecular genetic studies

Given the contribution of heritable factors to variation in gender identity, several studies appeared in the past decade focused on individual candidate genes. Most candidate gene studies have focused on sex-hormone receptors, such as androgen and oestrogen receptor genes, or genes involved in sex hormone pathways. To date, no conclusive associations have been identified [for an overview of candidate-gene studies in gender identity see (Fisher et al. 2017)]. As the genetic architecture of most complex human traits is characterized by very small effect sizes of multiple common genes,

the inconclusive results thus far are most likely due to the small sample sizes and focus on individual genes. An important next step to understanding the genetic background of the development of gender identity would be a sufficiently powered Genome Wide Association Study (GWAS), as this type of design has been proven to be successful for many other complex human traits (Visscher et al. 2017). We therefore strongly recommend gathering all genetic and phenotypic data on gender identity and gender dysphoria to date in order to perform a sufficiently powered GWAS in the near future. Very recently, Yang et al. (2017) investigated with a genetic sequencing design the effects of rare genetic variants in 14 Han Chinese self-identified transgender individuals. They identified an effect of *RYR3*, a gene that is highly expressed in the brain and regulates intracellular calcium homeostasis. However, given the very small sample size of this study, and the likely polygenic architecture of gender identity, this gene should be viewed as just one of many potentially contributing genetic factors instead of a major causal genetic mechanism. Moreover, replication of this finding is needed before any firm conclusion can be drawn on the association between *RYR3* and Gender Dysphoria.

Confronting stigma-related health disparities through community-engaged genomics research

A growing body of research demonstrates that gender minorities systematically experience worse social, economic, and health outcomes compared to cisgender people (Brown and Jones 2016; Fredriksen-Goldsen et al. 2014; Poteat et al. 2016; Reisner et al. 2016). Minority stress theory, which hypothesizes that poor outcomes among minority populations are due to the impact of identity-based stigma and systematic marginalization, provides the leading explanation for these disparities observed among gender minority populations (Bockting et al. 2013; Lick et al. 2013; Meyer 2003; Sevelius 2013; Testa et al. 2017). Examples of stigma that have been shown to negatively impact gender minorities include exclusion from public restrooms, public transportation, and health care systems (Reisner et al. 2015; White Hughto et al. 2015). Moreover, familial rejection due to stigma is a major cause of homelessness and attempted suicide among transgender youth (Mustanski and Liu 2013). Stigma itself is thought to emerge as a function of limited knowledge (ignorance), negative attitudes (prejudice), and negative behavior (discrimination) (Thornicroft et al. 2008). Consistent with this theoretical framework, a general lack of knowledge about the development of gender identity may be a contributing factor to societal stigma of gender minorities (Grant et al. 2011; Institute of Medicine 2011; McKay 2011; Reisner et al. 2016). In contrast, gender affirmation, family acceptance, and community support have been associated with better health outcomes among gender minority populations, including transgender youth (Bockting et al. 2016; Durwood et al. 2017; Hatzenbuehler and Pachankis 2016; Nuttbrock et al. 2002; Romijnders et al. 2017; Wesp and Deutsch 2017).

The healthcare setting is a critically important environment in which to reduce anti-transgender stigma and promote resilience through gender affirmation, yet, transgender people remain medically underserved (Winter et al. 2016; Wylie et al. 2016). Lack of provider knowledge and stigma towards transgender people have been identified as two primary barriers to care by transgender patients and their families, second only to lack of insurance coverage (Gridley et al. 2016; Nahata et al. 2017; Safer et al. 2016). For example, one recent study found that approximately 37% of endocrinologists in the MidAtlantic region of the United States are not willing to prescribe hormone therapy to transgender individuals, that only 41% described themselves as "somewhat" or "very" competent to provide transgender care (Irwig 2016) and another study showed that transgender patients continue to experience high rates of discrimination at the hands of medical professionals (Grant et al. 2011).

Emerging literature suggests that biomedical research can play an important role in reducing stigma by reducing blame among medical professionals and lay people (Dar-Nimrod and Heine 2011; Hoyt et al. 2017; Phelan 2005). However, opinions among ethicists and community members about the relative merits of employing "born this way" arguments to reduce stigma against gender minorities vary widely. In a recent article in the *American Medical Association Journal of Ethics*, Drs. Powell, Shapiro, and Stein criticize strategies that seek to advance equality for gender minorities by characterizing gender identity as "immutable, innate, and not chosen" as "vulnerable to attack on several grounds, including on the basis of emerging scientific data" (Powell et al. 2016). Instead, they argue for the adoption of a human rights framework to advance transgender equality (Powell et al. 2016). We agree that a biogenetic educational campaign should not replace a human rights framework, and propose that these two are not mutually exclusive.

Educational approaches that incorporate genetic knowledge have been successful in reducing negative stereotyping and stigma of several complex traits among medical professionals (Bannatyne and Stapleton 2015; Persky and Eccleston 2011). Importantly, these studies show that knowledge of biological influences on complex traits is a powerful tool to help healthcare providers alter their attitudes towards stigmatized populations. In addition, recent work has shown that, among lay people, educational interventions aimed at explaining the genetic contribution to obesity were not found to be harmful, as some had previously suggested (Dar-Nimrod and Heine 2011; Hoyt et al.

2017; Phelan 2005), but instead contributed to decreased stigmatization (Hilbert 2016). As another example, lesbian and bisexual women who believe that their sexual identities are innate have been found to have lower levels of self-stigma (Morandini et al. 2017). Studies of mental health traits have shown mixed effects of biogenetic explanations on stigma. In a meta-analysis of studies involving a total of 2326 participants (Kvaale et al. 2013), biogenetic explanations significantly reduced the inclination to blame individuals for their mental health needs. However, the authors also found that biogenic education interventions slightly increased the perception that people with mental illness (i.e., mood disorders, schizophrenia, etc.) are unpredictable and dangerous, demonstrating that explanation of biogenetic contributions to complex traits is not a panacea to stigma. Thus, there remain community concerns that genomic research into gender identity could increase stigma towards minority populations or be used against gender minorities in some way.

If research into understanding the genetic contribution to the development of gender identity is to proceed responsibly, it must be conducted within a community-engaged research (CER) framework to ensure the ethical and effective implementation of research to improve outcomes for gender minorities. CER includes building authentic partnerships between researchers and community members (Wilkins et al. 2013). Using a CER approach, researchers, community leaders, and members of marginalized populations collaboratively develop long-term, equitable partnerships to inform the design, conduct, and dissemination of research programs tailored to improve health equity. Community stakeholders and members, in addition to providing input about how to implement or even conceptualize scientific research designs, also provide essential expertise into the structure of political and social support systems and day-to-day life experiences of a marginalized group (Joosten et al. 2015). Ensuring this sharing of expertise between researchers and the community can result in a better balance between research and action for the mutual benefit of all partners engaged in the research and the community at large (Leshner et al. 2013).

Conclusion

This review of existing family and twin studies summarizes significant and consistent evidence for the role of innate genetic factors in the development of both cisgender and transgender identities, a negligible role for shared environmental factors, and a small potential role for unique environmental factors. Heritability estimates are consistent with other behavioral and personality traits, which generally fall in the range of 30–60% (Polderman et al. 2015). Additional studies with many more individuals are needed to determine the heritability of gender identity more precisely and to characterize the genetic architecture of gender identity through genome-wide association studies. Furthermore, we have provided evidence from other fields that this research can be used to reduce stigma, particularly among health care providers, though we caution that such efforts are not without some risk of increased stigma. Therefore, we join others in asserting that community-engaged research on the innate factors related to gender identity is essential to rapidly reduce health disparities among gender minorities and should be conducted *within* a human-rights framework and with support from government and academic partners (Winter et al. 2016).

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflicts of interest.

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Affiliations

Tinca J. C. Polderman[1,2] · Baudewijntje P. C. Kreukels[3,4] · Michael S. Irwig[5] · Lauren Beach[6,7] · Yee-Ming Chan[8,9] · Eske M. Derks[10] · Isabel Esteva[11,12] · Jesse Ehrenfeld[6,13,14,15,16] · Martin Den Heijer[4,17] · Danielle Posthuma[1,2] · Lewis Raynor[18] · Amy Tishelman[8,19] · Lea K. Davis[6,20,21,22,23] · on behalf of the International Gender Diversity Genomics Consortium

1 Department of Complex Trait Genetics, Vrije Universiteit, Amsterdam, The Netherlands

2 Center for Neurogenomics and Cognitive Research, Vrije Universiteit, Amsterdam, The Netherlands

3 Department of Medical Psychology, VU University Medical Center, Amsterdam, The Netherlands

4 Center of Expertise on Gender Dysphoria, VU University Medical Center, Amsterdam, The Netherlands

5 Division of Endocrinology, Center for Andrology, George Washington University, Washington, DC, USA

6 Program for LGBTI Health, Vanderbilt University Medical Center, Nashville, TN, USA

7 Division of Nephrology & Hypertension, Vanderbilt University Medical Center, Nashville, TN, USA

8 Division of Endocrinology, Department of Medicine, Boston Children's Hospital, Boston, MA, USA

9 Department of Pediatrics, Harvard Medical School, Boston, MA, USA

10 Translational Neurogenomics Group, QIMR Berghofer, Brisbane, QLD, Australia

11 Department of Endocrinology and Gender Identity Unit, University Regional Hospital of Malaga, Malaga, Spain

12 Foundation Institute of Biomedical Research in Malaga (FIMABIS-IBIMA), Malaga, Spain

13 Department of Anesthesiology, Vanderbilt University Medical Center, Nashville, TN, USA

14 Department of Surgery, Vanderbilt University Medical Center, Nashville, TN, USA

15 Department of Biomedical Informatics, Vanderbilt University Medical Center, Nashville, TN, USA

16 Department of Health Policy, Vanderbilt University Medical Center, Nashville, TN, USA

17 Department of Internal Medicine, VU University Medical Center, Amsterdam, The Netherlands

18 Department of Research, OCHIN, Inc., Portland, OR, USA

19 Divisions of Endocrinology and Psychiatry, Boston Children's Hospital, Boston, MA, USA

20 Division of Genetic Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

21 Department of Psychiatry and Behavioral Sciences, Vanderbilt University Medical Center, Nashville, TN, USA

22 Vanderbilt Genetics Institute, Vanderbilt University Medical Center, Nashville, TN, USA

23 23Vanderbilt University, 511-A Light Hall, 2215 Garland Ave, Nashville, TN 37232, USA